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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/875,305	06/05/2001	Victor J. Dzau	50025/003003	7095

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/875,305	DZAU ET AL.	
	Examin r	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/11/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This office action is in response to a Request for Continued Examination (RCE) filed 8/11/03 and an amendment filed 8/11/03. Claims 13-27 are pending. An IDS filed 8/11/03 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Priority

It is noted that this application appears to claim subject matter disclosed in prior copending Application No. 08/524,206, filed 9/8/1995. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). Also, the current status of all nonprovisional parent applications referenced should be included.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied

by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites a method for the prevention and treatment of NFκB-associated diseases or conditions in a mammal by introduction of an NFκB decoy into cells of the mammal. The invention utilizes disciplines of molecular biology and gene therapy.

2) Scope of the invention. This invention has broad scope in that it recites a method for the prevention and treatment of ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis or NFκB-associated disease. The broad and diverse nature of diseases that are considered NFκB-associated exacerbates the lack of disclosure for use of NFκB decoy in gene therapy and vaccination.

3) Number of working examples and guidance. The instant disclosure is directed to the broad field of decoy therapy. Decoy therapy is based upon blocking the capacity of endogenous trans-activating factors to modulate gene expression and thereby affecting the pathological processes associated with the transcription factors. While applicants provide guidance for a variety of decoys to be used in multiple diseases, the specific guidance relating to use of NFκB decoys for NFκB-associated diseases is a list of NFκB-associated diseases (page 6) that include ischemic reperfusion injury, inflammation, glomerulonephritis, immune response and transplant rejection. For administration of NFκB in decoy therapy the table on page 11 teaches that for inflammatory skin diseases and dermatitis topical application of polymer NFκB is preferred, for glomerulonephritis intravenous or intrarenal application of polymer or liposome NFκB is preferred. For myocoardial infarction intracoronary application of liposomes or polymers of NFκB is

preferred and for organ transplant intravascular or *ex vivo* application of liposomes or polymers in NFκB is preferred. Administration of E2F and NRE *in vitro* and *in vivo* to rats are presented. For NFκB, many parameters have not been addressed such as the NFκB dsDNA molecule to be used, the amount of DNA to be delivered, timing of administration, retention, and the stability of the NFκB decoy in the vessel walls.

4) State of Art. Decoy gene therapy in 1993 was not a tested art and the unpredictability of using this invention was high due to the lack of methods or processes for its use in humans. Furthermore, strategies to prevent or treat conditions of ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis - in humans at the time of invention did not include decoy gene therapy in 1993.

5) Unpredictability of the art. The art of preventing or treating NFkB-associated disease using decoy therapy is highly unpredictable. The lack of well defined targets (i.e. for whom the disease is prevented) compounded by the lack of disclosure for treatment with NF*k*B decoys makes it unpredictable as how to determine patients most likely to benefit from treatment, how to deliver to multiple targets, when to deliver, how to keep the drug in place long enough to achieve full activity and how to overcome the potential deleterious effects of inhibition of wound healing.

At the time of filing, the few *in vitro* assays with an NFkB binding element provided evidence in the prior art that decoy use *in vitro* has promise. However, *in vitro* and animal models have not correlated well with *in vivo* clinical trial results in patients. Since the therapeutic indices of NFkB decoy molecules can be species and model dependent, it is not clear that reliance on experimental models accurately reflects the

relative superiority or efficacy of the claimed therapeutic strategy. Multiple numbers of different pharmacological strategies to inhibit for example restenosis have proved futile (Popma et al 1991, page 1426 col. 1 first paragraph). "These disappointing results may be due in part to interspecies differences in the process of neointimal proliferation in humans and animal models or to the incomplete role of neointimal hyperplasia in the causation of human restenosis".

To date the process of treating and preventing disease in humans still remains highly unpredictable by any method. Morishita et al (2001 page 106, first paragraph) states, " current in vivo methods for vascular gene transfer are still limited by the lack of efficiency and potential toxicity." Various techniques that are recited for local administration (quoted below and also found on page 10, line 11-19) fall in a category that was in 1994 called "the potential Achilles' heel of biotechnology" (Lincoff, et al. page 2070 last full paragraph). The limitations, obstacles, disadvantages of the available local delivery devices are described by Lincoff page 2075, first paragraph –2078 2nd paragraph) and include for example the following which appears to summarize the section "Despite the intuitive simplicity of delivering drugs through a catheter... a number of obstacles must be overcome before such treatment becomes clinical reality. These may be summarized as follows: how to deliver, what to deliver, when to deliver, how to keep the drug in place long enough to achieve full activity, how to overcome the potential deleterious effects of inhibition of wound healing, how to identify patients most likely to benefit..." (page 2073 last paragraph). Applicants have not identified how to deliver, what to deliver, when to deliver, how to keep the drug in place long enough to achieve full activity, how to overcome the potential deleterious effects of inhibition of

wound healing, how to identify patients most likely to benefit increasing the unpredictability of a highly unpredictable art.

6) Summary. The invention recites a complex series of methods for preventing or treating multiple NFκB-associated diseases. The invention proposes as a method, the introduction of NFκB decoys, dsDNA molecules that bind to NFκB transcription factors, to inhibit their function in patients. Potential disease targets of this invention include those at risk of developing ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Independent claim 13 and by dependency claims 14-27 recite "A method for the prevention or treating an NFκB-associated disease". In addition to the reasons stated above, these claims are not enabled for prevention of NFκB-associated diseases. In

humans, the claimed diseases are usually established before therapy is offered. The specificity does not adequately teach how to effectively predict for whom the prevention would be required. In view of predictability of the art to which the invention pertains and the lack of established clinical protocols to predict for whom the therapies would be required: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in Applicant's for how to reasonably determine for what population the claimed invention is intended.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue experimentation and excessive experimentation in order to practice the claimed invention.

Response to Argument

Applicants state on page 3 of the amendment filed 8/28/03 that a Petition under 37 CFR 1.78(a)(3) for parallel Application No. 09/839,752 was dismissed as moot. According to the decision, the petition for priority information was not required as the priority information was provided in the transmittal letter and the Office noted the claimed priority in a filing receipt. The instant case also noted the claim for priority in a transmittal letter that was acknowledged by the Office and accordingly applicant request that the priority claim be acknowledged.

A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76). A priority

claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The response to the petition regarding 09/839,752 is not directed to the instant case and therefore cannot be considered in the instant case.

Applicants traverse the rejection of claims 13-27 under 35 USC 112, first paragraph, on pages 4-9 of the amendment filed 8/28/03. Applicants argue that the specification clearly teaches a set of NFκB-associated diseases or conditions and sufficient direction for administration of NFκB decoys. Applicants point to the disclosure that teaches that NFκB is released from inhibitors and as such is available in specifically activated cells and that "exemplary" NFκB-associated diseases or conditions are listed on page 6. The decoys are administered according to various techniques disclosed on pages 10 and tables 10-11. Applicants point to the prior art as teaching that there is evidence for the involvement of NFκB in disease pathology. Prior art references are provided detailing the role of NFκB in modulating i.e. cytokines and adhesion molecules involved in a variety of disease states. Finally, prior art references are provided that teach the efficacy of NFkB decoys in the treatment and prevention of NFkB-associated disease and conditions.

Applicant's arguments filed 12/16/02 have been fully considered but they are not persuasive. Details for *in vivo* use of NFκB decoys are not adequately taught in the specification. The instant invention does not teach methods for clinical or pre-clinical use of the proposed invention such that the instant invention can be used. Essential factors not taught include treatment intensity, accompanying immuno-suppression drugs

and schedule of treatment, amount of decoy and route of administration per specific disease as well as how to effectively predict for whom the prevention would be required.

Many of the prior art references details transfer of NFκB decoys cells *in vitro* into a variety of isolated cells in culture. For example, applicant cited reference by Griesenbach et al teach use of NFkB decoy in CFTE cultured cells (page 308). It is unclear if the *in vitro* data provided by applicant would be considered by the skilled artisan as being correlated with successful treatment of patients for allogeneic graft rejection.

Several post-filing prior art references provided by applicant teaches use of NFκB decoys *in vivo*. In these references, a variety of animal models are used. Sprague-Dawley rats were used as animal models for treatment of neointima formation (Yoshimura et al), for autoimmune myocarditis (Yokoseki et al), for brain ischemia (Ueno et al), for ischemia-reperfusion injury (Sawa et al), for a neuropathic pain model (Sakaue et al) and for apoptotic cell detection (Matsushita et al) with HVJ-liposomes containing NFkB decoy molecules. This model was also used in ex vivo treatment of coronary artery disease and heterotropic heart transplants using hyperbaric pressure mediated transfection of dsDNA (Feeley et al). While a canine aortocoronary by-pass grafting model were used as animal models for treatment of neointima formation using pressure-mediated transfection methods with dsDNA (Shintani et al). Wistar rats were used as animal models for treatment of experimental cresentic glomerulonephritis (Tomita et al) and for vascular inflammation (Kitamoto et al) with HVJ-liposomes containing NFkB decoy molecules and for inflammation following injection intradermally with dsDNA. An NC/NGA mouse model was used as a model for

dermatitis treatment and prevention using dsDNA topically applied (Nakamura et al). Murine cardiac allografts were used in animal models for treatment of transplant rejection (Suzuki et al) with HVJ-liposomes containing NFkB decoy molecules. New Zealand White rabbits were used in a cerebral angiopathy model with a cationic liposome complex administered through the cerebrospinal fluid (Ono et al) and a preclinical study using pigs for a myocardial injury model with DNA-liposomes (Kupatt et al). Applicant presents no art-recognized nexus between the results obtained in the prior art and the results the skilled artisan would expect to see in humans. Furthermore, any successes recited in the cited papers cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of said references. The instant specification teaches, "Optimal treatment parameters will vary with the indication, decoy, clinical status, etc. and are generally determined empirically, using the guidance provided herein." (page 10, line 21-23). **This guidance is general and broad** for the use of NFκB decoys and these teachings in no way provide the skilled artisan with the ability to use the decoys to treat a patient with or at risk of developing ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis. No *in vivo* protocol steps or teachings are provided for NFκB decoys in the specification. Therefore, the teaching of the specification and prior art do not teach one how to use the NFκB decoys for therapeutic purposes in humans or how to prevent the occurrence of each of the diseases or conditions.

Additionally, we have no guidance as to how to effectively predict for whom the prevention would be required. In view of the unpredictability of the art to which the

invention pertains and the lack of established animal models that correlate to human disease patient with or at risk of developing ischemic reperfusion injury, myocardial infarction, inflammation, glomerulonephritis, dermatitis, immune disease, transplant rejection, neoproliferative disorder or restenosis and the lack of clinical protocols: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description for how to reasonably determine how to use the claimed cellular compositions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucell, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Patent analyst Kay Pinkney whose telephone number is (703) 305-3553.

Donald R. Leffers

GERRY LEFFERS
PRIMARY EXAMINER

Maria B Marvich, PhD
Examiner
Art Unit 1636

November 12, 2003